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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,447	12/12/2005	Ulf Gyllensten	25401-39	2553

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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,447	GYLLENSTEN ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This supplemental Office Action is in response to the traversal of the restriction of nucleotide sequences, as was discussed in a phone interview with Applicant's agent on July 10, 2007. The restriction of nucleotide sequences generic to claim 9 has now been modified to include SEQ ID NOS. 3-8 representing primers and SEQ ID NOS. 22-24 representing probes, with the previously elected SEQ ID NOS. 1, 2, 9, 10, 21 and 25.

The previous requirement for restriction of invention groups is still deemed proper and the restriction is therefore made FINAL.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gissmann et al. (U.S. Patent No. 6,228,368) in view of Goldsborough et al. (GenBank Accession No. J04353, 1994) and further in view of Seedorf et al. (EMBO J. (1987) 6:139-144) and futher in view of Sastre-Garau et al. (J. Gen. Virol. (2000) 81:1983-1993 and GenBank Accession No. AJ242956) and further in view of Marich et al. (Virology (1992) 186:77-776 and GenBank Accession No. M74117) and further in view of Buck et al. (BioTechniques (1999) 27:528-536).

With regard to claim 9, Gissmann teaches a sequence that can be used for designing primers SEQ ID NO: 1 and SEQ ID NO: 2, and the probe SEQ ID NO: 21 for detection and quantification of HPV 16 (positions 91-111 of SEQ ID NO: 3 of Gissmann is homologous to SEQ ID NO: 1, positions 168-146 of SEQ ID NO: 3 of Gissmann is homologous to SEQ ID NO: 2, and positions 121-142 of SEQ ID NO: 3 of Gissmann is homologous to SEQ ID NO: 21).

Gissmann does not teach a kit comprising the amplification primers of SEQ ID NOS: 3-10, and the probes of SEQ ID NOS: 22-25, for HPV 18, 31, 35 and 45.

With regard to claim 9, Goldsborough teaches a sequence that can be used for designing primers SEQ ID NO: 3 and SEQ ID NO: 4 and the probe SEQ ID NO: 22 for detection and quantification of HPV 31 (positions 476-497 of J04353 of Goldsborough is homologous to SEQ ID NO. 3, positions 556-533 of J04353 is homologous to SEQ ID NO: 4, and positions 529-507 of J04353 is homologous to SEQ ID NO: 22).

Goldsborough does not teach a kit comprising the amplification primers of SEQ ID NOS: 1, 2 and 5-10, and the probes of SEQ ID NOS: 21 and 23-25, for HPV 16, 18, 35 and 45.

With regard to claim 9, Seedorf teaches a sequence that can be used for designing primers SEQ ID NO: 5-7 and the probe SEQ ID NO: 23 and 24 for detection and quantification of HPV 18 (positions 1093-1113 of Seedorf, Figure 1a is homologous to SEQ ID NO: 5/6, positions 1168-1148 is homologous to SEQ ID NO: 7, and positions 1115-1140 is homologous to SEQ ID NO: 23/24).

Seedorf does not teach a kit comprising the amplification primers of SEQ ID NOS: 1-4 and 8-10, and the probes of SEQ ID NOS: 21, 22 and 25, for HPV 16, 31, 35 and 45.

With regard to claim 9, Sastre-Garau teaches a sequence that can be used for designing primers SEQ ID NO: 8 for detection and quantification of HPV 45 (positions 7185-7164 of AJ242956 of Sastre-Garau is homologous to SEQ ID NO: 8).

Sastre-Garau does not teach a kit comprising the amplification primers of SEQ ID NOS: 1-7, 9 and 10, and the probes of SEQ ID NOS: 21-25, for HPV 16, 18, 31 and 35.

With regard to claim 9, Marich teaches a sequence that can be used for designing primers SEQ ID NO: 9 and SEQ ID NO: 10, and the probe SEQ ID NO: 25 for detection and quantification of HPV 35 (positions 3365-3382 of the HPV 35 sequence taught by Marich is homologous to SEQ ID NO: 9, positions 3468-3451 of the sequence taught by Marich is homologous to SEQ ID NO; 10, and positions 3398-3427 of the sequence taught by Marich is homologous to SEQ ID NO: 25).

Marich does not teach a kit comprising the amplification primers of SEQ ID NO: 1-8 and the probes of SEQ ID NO: 21-24, for HPV 16, 18, 31 and 45.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to utilize the sequences taught by Gissmann, Goldsborough, Seedorf, Sastre-Garau and Marich in order to design amplification primers and probes for a kit to detect and quantitate HPV in a type-specific manner. Thus, an ordinary practitioner would have been motivated to use such sequences in order to design primers and probes that are specific for particular HPV types, especially high-risk types such as HPV 16, 18, 31, 35 and 45 associated with cervical cancer.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Gissmann, Goldsborough, Seedorf, Sastre-Garau and Marich, which are 100% derived from sequences expressly suggested by the prior art of Gissmann, Goldsborough, Seedorf, Sastre-Garau and Marich as useful for primers for

the detection and quantitation of human papillomavirus, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned

as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

5. Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gissmann et al. (U.S. Patent No. 6,228,368) in view of Marich et al. (Virology (1992) 186:77-776 and GenBank Accession No. M74117) and further in view of Yoo et al. (Genomics (1993) 15:21-29 and GenBank Accession No. M95623) and further in view of Buck et al. (BioTechniques (1999) 27:528-536).

Gissmann, Marich and Buck together teach the limitations of claim 9 as discussed above.

Neither Gissmann, Marich nor Buck teach amplification primers SEQ ID NO:19 and SEQ ID NO:20 and the probe SEQ ID NO:30, for detection and quantification of the amount of the human single copy gene hydroxymethylbilane synthase (HUMPBGDA).

With regard to claims 10 and 11, Yoo teaches a sequence that can be used for designing primers SEQ ID NO:19 and SEQ ID NO:20, and the probe SEQ ID NO:30 for detection and quantification of the human single copy gene HUMPBGDA (positions

4750-4770 of the PBGD sequence taught by Yoo is homologous to SEQ ID NO. 19, positions 4868-4850 of Yoo is homologous to SEQ ID NO. 20, and positions 4788-4813 of Yoo is homologous to SEQ ID NO. 30).

Yoo does not teach primers for detection and quantification of HPV 16 or HPV 35.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to utilize the sequences taught by Yoo in order to design amplification primers and probes for a kit to detect and quantitate human PBGD. Thus, an ordinary practitioner would have been motivated to use such sequences in order to design primers and probes that are specific for a single-copy human PBGD gene which can be used for determining cell-copy number for more accurate detection and quantification of human papillomavirus such as the high-risk types of HPV 16 and 35 associated with cervical cancer.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoo, which are 100% derived from sequences expressly suggested by the prior art of Yoo as useful for primers for the detection and quantitation of human PBGD and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked

(see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

6. Claims 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gissmann et al. (U.S. Patent No. 6,228,368) in view of Marich et al. (Virology (1992) 186:77-776 and GenBank Accession No. M74117) and further in view of Swan et al. (J. Clin. Microbiol. (1997) 35:886-891) and further in view of Buck et al. (BioTechniques (1999) 27:528-536).

Gissmann, Marich and Buck together teach the limitations of claim 9 as discussed above.

Neither Gissmann, Marich nor Buck teach a kit comprising at least two different fluorophores for detection and diagnosis of cervical cancer.

With regard to claims 12 and 14, Swan teaches a type-specific fluorogenic probe assay for detection and quantitation of HPV, including high-risk types associated with

cervical cancer, using probes containing FAM or HEX and a rhodamine quencher dye, TAMRA (p. 886, column 1, lines 1-5, lines and column 2, lines 7-25).

Swan does not teach sequences that allow for the designing of primers and probes for detection and quantification of HPV 16 or HPV 35.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Gissmann, Marich and Buck that teach sequences to allow designing of primers and probes for a kit for detection and quantification of HPV 16 or HPV 35 with those of Swan that teach the use of fluorogenic probes for detecting and quantitating high-risk HPV types since the probes can all be readily prepared with fluorescent labels during synthesis using the necessary phoshoramidites and esters (Swan, p. 886, column 2, lines 16-25). Thus, an ordinary practitioner would have been motivated to use HPV sequences in order to design primers and fluorescently-labeled probes to provide a fast, simple and highly sensitive method to detect and type HPV DNA, since the probe is present in the PCR reaction mixture to allow direct measurement of fluorescence after PCR without further manipulations (Swan, p. 890, column 1, line 13 to column 2, line 5).

7. Claims 13 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gissmann et al. (U.S. Patent No. 6,228,368) in view of Marich et al. (Virology (1992) 186:77-776 and GenBank Accession No. M74117) and further in view of Yoo et al. (Genomics (1993) 15:21-29 and GenBank Accession No. M95623) and further in view of Swan et al. (J. Clin. Microbiol. (1997) 35:886-891) and further in view of Buck et al. (BioTechniques (1999) 27:528-536).

Gissmann, Marich, Yoo and Buck together teach the limitations of claims 10 and 11 as discussed above.

Neither Gissmann, Marich, Yoo nor Buck teach a kit comprising three different fluorophores for detection and diagnosis of cervical cancer.

With regard to claims 13 and 18-20, Swan teaches a type-specific fluorogenic probe assay for detection and quantitation of HPV, including high-risk types associated with cervical cancer, using probes containing FAM or HEX and a rhodamine quencher dye, TAMRA (p. 886, column 1, lines 1-5, lines and column 2, lines 7-25).

Swan does not teach sequences that allow for the designing of primers and probes for detection and quantification of HPV 16 or HPV 35. Swan also does not teach amplification primers SEQ ID NO:19 and SEQ ID NO:20 and the probe SEQ ID NO:30, for detection and quantification of the amount of the human single copy gene hydroxymethylbilane synthase (HUMPBGDA).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Gissmann, Marich, Yoo and Buck that teach sequences to allow designing of primers and probes for a kit for detection and quantification of HPV 16 or HPV 35 as well as that of a house-keeping gene, PBGD, with those of Swan that teach the use of fluorogenic probes for detecting and quantitating high-risk HPV types since the HPV and PBGD probes can all be readily prepared with fluorescent labels during synthesis using the necessary phoshoramidites and esters (Swan, p. 886, column 2, lines 16-25). Thus, an ordinary practitioner would have been motivated to use HPV and PBGD sequences in order to design primers and

fluorescently-labeled probes to provide a fast, simple and highly sensitive method to detect and type HPV DNA, since the probe is present in the PCR reaction mixture to allow direct measurement of fluorescence after PCR without further manipulations (Swan, p. 890, column 1, line 13 to column 2, line 5). Furthermore, primers and a probe for a housekeeping gene such as PBGD or β-globin (used by Swan) can be used to normalize the HPV signal to improve quantitation, since this allows samples with unequal DNA content or reaction inhibitors to be measured accurately (Swan, p. 890, column 2, lines 28-36).

Conclusion

8. Claims 9-14 and 18-20 are rejected. No claims are allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas 8/18/07

David C. Thomas
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
8/14/07